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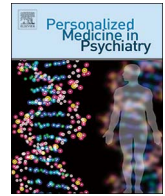
Early treatment response affects signal detection in a placebo-controlled depression study

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ABSTRACT

We examined the effect of early treatment response on the Quick Inventory of Depressive Symptomatology (QIDS-SR$_{16}$) within 2 weeks following randomization on the eventual treatment outcome at 6 weeks in a double-blind study of subjects with major depressive disorder randomly assigned to a combination treatment (buspirone 15 mg with melatonin SR 3 mg), buspirone 15 mg, or placebo (Clinicaltrials.org: NCT 007005003).

The extent of QIDS-SR$_{16}$ score improvement between baseline and week 2 was significantly associated with higher treatment response rates at week 6 ($\geq$50% QIDS-SR$_{16}$ improvement from baseline) regardless of treatment assignment.

Thirty-two of 123 subjects (26.0%) were QIDS-SR$_{16}$ treatment responders by week 2 and were excluded in a post-hoc analysis of five clinical metrics: QIDS-SR$_{16}$, the Inventory of Depressive Symptomatology (IDS-c30), clinical global impression of severity and improvement scales, and Hamilton rating scale for anxiety.

The effect size favoring the combination-treatment over buspirone and/or placebo increased on each of the 5 clinical metrics in the remaining 91 subjects with < 50% QIDS-SR$_{16}$ improvement at week 2. For instance, the effect size favoring the combination treatment over the pooled buspirone and placebo groups improved from 0.33 in the mITT population to 0.64 for the QIDS-SR$_{16}$, and from 0.37 to 0.58 for the IDS-c30. Further, the statistical significance favoring the combination treatment improved from p = .055–.017 for the QIDS-SR$_{16}$.

This was a post-hoc analysis of a small MDD study, but it is clear that future studies need to explore the mediating factors that affect signal detection and influence individual treatment response.

Introduction

The achievement of signal detection is particularly challenging in trials of major depressive disorder (MDD) where the placebo response has increased over the past three decades [1–5].

The inherent conditions of the clinical trial itself may facilitate symptomatic improvement and impede the detection of a true drug effect [4–15]. The informed consent process differentiates the willing from the unwilling subject, and the decision to consent may foster unrealistic expectations about the treatment outcome. The perception of illness severity, possible frustration about previously unsuccessful treatment interventions, or a sense of urgency for help may motivate some potential study subjects to exaggerate their symptoms to qualify for a clinical trial. Some site-based raters may inflate some rating scores in order to achieve study eligibility thresholds [16]. Further, a study subject may respond to queries differently as he or she gains increasing familiarity with the questions that measure symptom severity, and the natural course of the acute major depressive episode (MDE) may

contribute to clinical improvement during the clinical trial [8]. Regardless of the etiology, the severity of each individual's depressive symptoms often attenuates shortly after the randomization visit regardless of treatment assignment, which may impede signal detection [2–3,5–8,17].

Early symptomatic improvement may influence the eventual treatment response [2–6,17–21]. In a meta-analysis of 4 randomized, double-blind, placebo-controlled depression trials, Evans and colleagues reported that improvement of the pre-randomization scores of the Hamilton rating scale for depression (HamD$_{17}$) between screen and baseline was associated with a higher placebo response rate and poorer drug–placebo separation at the end of these trials [19]. In an analysis of 8 double-blind MDD trials, Altin and colleagues reported that a 20% improvement of the total HamD$_{17}$ score within 2 weeks post-randomization yielded higher response and remission rates in both the duloxetine and placebo treated groups than in the subjects with < 20% improvement [20]. Thus, early symptomatic improvement may obscure the true drug effect and impede signal detection in clinical trials.

We examined the impact of early symptomatic improvement on eventual treatment outcome in a small, phase II clinical trial of subjects with major depressive disorder (MDD) who received a combination treatment of buspirone 15 mg with melatonin sustained release (SR) 3 mg. In pre-clinical studies, neurogenesis-based data has suggested that low buspirone doses (15 mg) combined with melatonin might yield an antidepressant effect [22]. We have previously reported that this combination treatment was significantly better than a pooled group of buspirone 15 mg and placebo-assigned subjects on the primary measure, the clinical global impression of improvement (CGI-I) scale, but not on the patient-rated Quick Inventory of Depressive Symptomatology (QIDS-SR$_{16}$) score [23–26].

For the current post-hoc analysis, the extent of the QIDS-SR$_{16}$ score improvement within 2 weeks of randomization was used to examine subsequent treatment outcome in this study. We found that early symptomatic improvement of the QIDS-SR$_{16}$ score within 2 weeks of randomization was associated with markedly higher treatment response rates across all treatment assignments and that early treatment response actually impeded signal detection.

Material and methods

Study design and study participants

This analysis was done as part of an investigator initiated clinical trial (CBM-IT-01; BCI NCT 007005003) conducted by the Clinical Trials Network at Massachusetts General Hospital and funded by BrainCells Inc. (San Diego, California). The methods and overall results of this study have been described elsewhere [25,26]. The core study was a randomized, 6-week, double-blind, placebo-controlled evaluation of a combination treatment of buspirone 15 mg combined with melatonin sustained release (SR) 3 mg) in patients with Major Depressive Disorder (MDD). Eligible subjects were randomized at baseline (Week 0) to receive either the combination treatment, buspirone 15 mg as monotherapy, or placebo in a 2:1:1 ratio for 6 weeks. Post-randomization study visits were done at weeks 2, 4, and 6 (the study endpoint).

The primary efficacy measures were the CGI-I and QIDS-SR$_{16}$ [23,24]. Subjects required a QIDS-SR$_{16}$ score ≥14 at screen and baseline for study eligibility.

Secondary variables included the Clinical Global Impression of Severity (CGI-S), Hamilton Rating Scale for Anxiety (Ham-A) and the Inventory of Depressive Symptomatology-30 item clinician version: IDSc30 [23,27,28]. Site-based raters administered the CGI-S at every study visit (screen, baseline, and weeks 2, 4, and 6. The IDSc30 and Ham-A instruments were administered at baseline and week 6 only.

All potential study subjects agreed in writing to participate in the study after reading and reviewing the IRB-approved informed consent.

All sites obtained IRB approval prior to initiating the study.

Subjects between 18 and 65 years of age who met DSM-IV-TR criteria for major depressive disorder (MDD), as determined by the Mini-International Neuropsychiatric Interview (M.I.N.I.) and psychiatric evaluation were eligible for this study [29,30]. Female patients of childbearing potential needed to be taking a reliable, medically acceptable form of contraception for at least 30 days prior to screening and throughout the study. Subjects meeting criteria for other Axis-I disorders as their primary diagnosis, had a history of eating disorders, obsessive-compulsive disorder, psychotic disorder, bipolar disorder and/or mental retardation and those with alcohol or substance abuse or dependency were excluded from the study. The use of antidepressant, antipsychotic, or anxiolytic medications or drugs with known psychotropic properties was prohibited for 1 week (4 weeks for fluoxetine) prior to screening and throughout the study. Subjects who used substances that are known inhibitors or inducers of CYP3A4 were also excluded.

142 patients meeting DSM-IV-TR criteria for MDD confirmed by the M.I.N.I. and meeting minimum QIDS-SR$_{16}$ score criteria (≥14) were enrolled in this study from 9 clinical trial sites located within the United States. This post-hoc analysis was conducted with the 123 subjects in the modified intent to treat (mITT) population with QIDS-SR$_{16}$ assessments completed at week 2.

Statistical analyses

We examined the effect of QIDS-SR$_{16}$ score improvement within 2 weeks of randomization on the eventual treatment outcome of all clinical metrics at the study endpoint. Treatment response at the study endpoint (week 6 or the last observation carried forward, LOCF) was defined as ≥50% QIDS-SR$_{16}$, IDSc30 or Ham-A total score improvement from the baseline visit.

Statistical analyses used an analysis of covariance (ANCOVA) model, with change from baseline as the dependent variable, the baseline value as a covariate, and treatment group as the factor with three values (placebo, buspirone, and the combination treatment). Additional analyses included X^2 tests with Yates correction for continuity and Cohen's d for effect size analyses where appropriate [31].

By design, the planned statistical analyses for this small study included a secondary pooling of the buspirone and placebo treatment groups on the expectation that these groups would not differ on the mean CGI-I at endpoint by more than 0.04 points [25]. This expectation was in fact realized, as the CGI-I score difference between buspirone and placebo was 0.04 at week 6. Thus, the buspirone and placebo groups were subsequently pooled for further ANCOVA and treatment response analysis against the combination treatment.

Table 1
Demographic and baseline clinical characteristics of MDD subjects.

	mITT Population	Combination[1]	Buspirone[2]	Placebo
n	123	60	31	32
Age (all) Mean ± SD	42.4 ± 12.0	43.3 ± 12.1	40.7 ± 12.3	42.2 ± 11.8
Gender (Female)%	82 (66.7%)	40 (66.7%)	19 (61.2%)	23 (71.9%)
Weight (lbs.)	203.9 ± 54.0	201.9 ± 56.5	215.8 ± 57.0	196.0 ± 54.3
BMI[3]	32.7 ± 8.3	32.2 ± 8.4	34.8 ± 9.1	31.6 ± 7.00
Baseline Clinical Metrics				
CGI-S (Mean ± SD)	4.50 ± 0.58	4.50 ± 0.60	4.55 ± 0.57	4.44 ± 0.56
IDSc30	41.3 ± 8.0	41.2 ± 8.1	42.3 ± 7.2	40.4 ± 8.7
QIDS-SR$_{16}$	17.1 ± 3.0	17.1 ± 3.1	17.0 ± 2.3	17.3 ± 3.4
Ham-A	20.1 ± 5.8	19.8 ± 6.0	20.2 ± 5.6	20.5 ± 5.6

[1] Combination treatment of buspirone 15 mg with melatonin 3 mg-SR.

[2] Buspirone monotherapy 15 mg daily.

[3] BMI = body mass index defined as weight (kg) divided by the subject's height in meters squared (m^2).